

REMARKS

STATUS OF THE CLAIMS

Claims 1-20 are pending. By this Reply, no claim amendments have been made and no new matter has been added.

REJECTION UNDER 35 U.S.C. § 102(b)

The Examiner maintains the rejection of claims 1-7 and 9-12 under 35 U.S.C. § 102(b) over Furuta *et al.*; *Jpn. J. Cancer Chemother*, 18(3):393-402, 1991 (hereinafter "Furuta"). The Examiner argues that Furuta discloses Applicant's composition "wherein said composition provides a synergistic effect in the treatment of tumors." Final Office Action at 2. In order to anticipate a claim, a reference must contain all elements of the claim. *See Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986). Applicant respectfully traverses the rejection and submits that Furuta does not anticipate the claimed invention.

A. Synergy

The Examiner previously provided two definitions of synergy and relied on these definitions to argue that the examples in Furuta demonstrate a synergistic effect, as presently claimed. However, the Examiner's reliance on these definitions is improper.

As the Examiner is aware, an Applicant may be his own lexicographer and define what she regards as the invention essentially in whatever terms chosen so long as the terms are not used in ways that are contrary to accepted meanings in the art. M.P.E.P. § 2173.01. An Applicant does not need to use the terminology used in the prior art so long as the terms used to define the invention are clear and precise. M.P.E.P. § 2173.05(a). "When the specification states the meaning a term in the claim is

intended to have, the claim is examined using that meaning." *Id.* (emphasis added), citing *In re Zletz*, 893 F.2d 319, 13 U.S.P.Q.2d 1320 (Fed. Cir. 1989). "When there is more than one definition for a term, it is incumbent upon applicant to make clear which definition is being relied upon to claim the invention." *Id.*

Applicant is presently claiming a synergistic therapeutic pharmaceutical composition that provides a synergistic effect in the treatment of solid tumors. Applicant has defined a synergistic effect as a combination of two constituents wherein the combination provides a therapeutic effect that is superior to one or the other of the constituents when used at its optimum dose (*i.e.*, maximum tolerated dose or highest non-toxic dose (HNTD)). Present application page 5, second full paragraph. This definition can also be found in an art recognized journal article (the Corbett article cited in the specification) and is therefore not contrary to accepted meanings in the art.

Moreover, Applicant consistently used this definition throughout the specification and examples further emphasizing that this definition is relied upon in the presently claimed invention. For example, the specification at page 6, second paragraph, discloses that "the maximum tolerated dose of the CPT-11/doxorubicin combination is therapeutically superior to the maximum tolerated dose of either CPT-11 or doxorubicin alone." Moreover, the combination of CPT-11 and doxorubicin produced "a therapeutic response [that] was better than for the agents alone." *Id.* at page 9, Table III, and last full paragraph; *see also*, Table IV on pages 11-12; the first full paragraph on page 13; and page 15, first paragraph.

In the Advisory Action dated July 11, 2003, the Examiner further argues that the term synergy as recited in the claims "does not suggest or imply any other meaning other than the ordinary and customary established meaning that is given in objective

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sources of information like dictionaries, encyclopedias, and treatises.” (Advisory Action at 2.) Moreover, the Examiner argues that a “term used in claims bear [sic] a ‘heavy presumption’ that they mean what they say and have the ordinary meaning that would be attributed to those words by persons skilled in the art.” (*Id.*, citing *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359 (Fed. Cir. 2002).)

As indicated above, the Examiner relies on *CCS Fitness* for the proposition that there is a “heavy presumption” that a claim term will have the “ordinary meaning that would be attributed to those words by persons skilled in the art.” (*Id.*) The Examiner has improperly relied on one sentence in this case without regard to other statements made by the court.

The claims at issue in *CCS Fitness* recited “reciprocating member.” (*CCS*, at 1363.) The appellee argued that the term “member” was a “vague term whose scope requires clarification from the specification and drawings.” (*Id.* at 1364.) In interpreting the claim, the court stated that “[g]enerally speaking, we indulge a ‘heavy presumption’ that a claim term carries its ordinary and customary meaning.” (*Id.* at 1365, citing *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985, 989 (Fed. Cir. 1999).) However, the court stated that this presumption may be overcome in at least four ways. (*Id.*)

First, the claim term will not receive its ordinary meaning if the patentee acted as his own lexicographer and clearly set forth a definition of the disputed claim term in either the specification or prosecution history. Second, a claim term will not carry its ordinary meaning if the intrinsic evidence shows that the patentee distinguished that term from prior art.

(*Id.*, at 1366, internal citations omitted.)

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The court held that the appellee did not show anything in the specification or prosecution history to overcome the “heavy presumption” and therefore the claim term “member” was given its ordinary and customary meaning.

The facts in the present application are different from those in *CCS Fitness*. In particular, Applicant has overcome the heavy presumption that the term “synergy” should be given its ordinary and customary meaning, such as the two dictionary definitions relied upon by the Examiner. In particular, Applicant has acted as her own lexicographer as previously argued in the Request for Reconsideration After Final Rejection filed May 21, 2003. (*See also Abbott Laboratories v. Novopharm Ltd.*, 323 F.3d 1324 (Fed. Cir. 2003) (holding that patentee had overcome the presumption that a claim term is given its ordinary and customary meaning because patentee acted as his own lexicographer by providing a definition in the specification).)

Moreover, Applicant has presented arguments, such as those below, distinguishing the claimed invention over the cited art, Furuta, by relying on the definition of synergy as defined in the present specification. In essence, Applicant has overcome the heavy presumption in two of the four ways discussed by the court in *CCS Fitness*. For this reason, we believe that the Examiner’s reliance on the cited case is misplaced and, in fact, supports Applicant’s position.

Because Applicant provided, in the specification and examples, a clear and precise definition of synergistic effect, and relied on this definition to distinguish over the cited art, the Examiner must examine the claims in view of this definition and not in view of other definitions.

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B. Furuta Does Not Anticipate the Claimed Invention

Although Furuta states that treatment with CPT-11 and adriamycin (*i.e.*, doxorubicin) provides synergistic effects, this reference does not, in fact, disclose a synergistic effect as defined in the present specification and presently claimed.

When using one constituent, such as CPT-11, one of ordinary skill in the art would expect that the best result would be achieved at the HNTD for that constituent. However, it may be beneficial to a patient to use a smaller dose, possibly, for example, to limit side effects. A synergistic combination allows a patient to receive a smaller dose (*i.e.*, less than the HNTD) of one or both constituents and provides results greater than would have been achieved with the HNTD if each constituent had been used individually.

Applicant determined the HNTD for CPT-11 by intravenous (i.v.) and oral routes on various tumors.¹ See page 7, Table I. The HNTD for CPT-11 per os (p.o.) was found to be 806.4 mg/kg (100.8 x 2 times per day x 4 days (6-9)) on PO3 tumors on B6D2F1 mice. See page 11, Table IV.

Additionally, Applicant determined the HNTD for doxorubicin by i.v. on PO3 tumors to be 12.4 mg/kg (6.2 x 2 days of administration). See page 11, Table IV. This result is also consistent with what is known in the art. See, for example,

¹ In the clinic, CPT-11 is generally administered by i.v. and oral routes. The HNTD for CPT-11 by i.v. was found to be 346.2 mg/kg on PO3 tumors on B6D2F1 mice. See page 7, Table 1. This HNTD is consistent with what is known in the art. See, for example, Chatelut, G. S., *et al.*, Comparison of Intraperitoneal and Intravenous Administration of Irinotecan (CPT-1) in a Murine Peritoneal Colon 26 Model, *Proc. Am. Assoc. Cancer Res.*, 38(3):305 (1997), copy attached. This reference reported the HNTD of CPT-11 by i.v. administration to be 300 mg/kg. Moreover, the HNTD for intraperitoneal (i.p.) administration of CPT-11 in mice having colon tumors was determined to be 600 mg/kg. See Chatelut abstract.

Kolfschoten, G. M., *et al.*, Development of a Panel of 15 Human Ovarian Cancer Xenografts for Drug Screening and Determination of the Role of the Glutathione Detoxification System, *Gynecologic oncology*, 76(3):362-8 (2000), copy attached. This reference reported the HNTD for doxorubicin by i.v. on human ovarian cancer to be 16 mg/kg (8 mg/kg x 2).

After determining the HNTD for each constituent, Applicant combined the constituents to determine if there was a synergistic effect, *i.e.*, whether smaller doses of each individual constituent could be used in a composition and yet still achieve a result better than the HNTD of one of the individual constituents when used alone. Applicant demonstrated such a synergistic effect in several combinations reported in Table IV on page 11 of the specification.

Furuta does not teach the HNTD dose for each individual constituent. In fact, Furuta determined the dose for each constituent not based upon the HNTD for each constituent, but instead used amounts that would produce a desired result, around 150 of the life prolonging rate T/C (%). See page 394, first paragraph. For example, Furuta determined that a dose of 37.5 mg/kg (12.5 x 3 days of administration on days 1, 5, 9) of CPT-11 by i.p. administration in mice having L1210 (leukemia) tumors achieved that goal. See Table 3. (Applicant notes that this dose is 1/16th of the reported HNTD for i.p. administration of CPT-11 in mice having colon cancer. See footnote 2.) Similarly, Furuta determined that a dose of 18.75 mg/kg (6.25 x 3 days of administration on days

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1, 5, 9) of doxorubicin i.p. administered in mice having L1210 (leukemia) tumors achieved that goal.²

The Examiner argues that the data in Table 3 "shows that the effect of two chemicals on the inoculated mice is greater than the effect of each of these chemicals individually" and refers to the example having 37.5 mg/kg CPT-11 (12.5 x 3 days of administration) and 18.75 mg/kg of adriamycin (6.25 x 3 days of administration) producing 16.5 days of survival as exhibiting a synergistic effect. See Office Action at 7 and Experiment 1 in Table A below. Applicant respectfully submits that the Examiner's statement is inconsistent with Applicant's definition of synergistic effect.

Moreover, Applicant respectfully submits that the Examiner's statement is not supported by all, and is contrary to some, of the data in Furuta. For ease of understanding, Applicant refers to Table A below. The Examiner's statement that the effect of two chemicals is greater than the effect of each is true for experiment 1, wherein the days of survival is greater when two chemicals are used than the effect of each of these chemicals used individually (experiments 2 and 3). However, the Examiner's statement is contrary to the data in experiment 4 when it is compared to the data in experiment 3. In experiment 4, both chemicals are used and the days of survival is 11.7. In experiment 3, only doxorubicin is used and the days of survival is 11.7. The data suggests that regardless of whether two chemicals are used, so long as doxorubicin is used, the days of survival is the same. The data does not appear to

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2 The HNTD for i.p. administration of doxorubicin in mice having lung carcinoma was determined to be 15 mg/kg. See Schmid, *et al.*, Differential Uptake of 1-(2-chloroethyl)-3-(trans-4-methylcyclohexyl)-1-nitrosourea and Doxorubicin by Lewis Lung Carcinoma and Ridgway Osteogenic Sarcoma, *Cancer-Res*, 43(3):976-9 (1983), copy attached.

suggest a synergistic effect, as defined by the Examiner or, for that matter, the Applicant.

Table A. Compilation of Data from Four Experiments in Furuta

Experiment	Total Dose of CPT-11 (12.5 mg/kg x 3 days of administration at days 1, 5, 9)	Total Dose of adriamycin (6.25 mg/kg x n days of administration)	Days of Survival
1	37.5	18.75, n=3	16.5
2	37.5	0	10.8
3	0	18.75, n=3	11.7
4	37.5	6.25, n=1	11.7

As further evidence that Furuta does not teach a synergistic combination, Applicant refers the Examiner to the rate of survival of the mice in Furuta. Applicant notes that in experiments 2 and 3 in Table A above, the mice treated with one constituent survived about 12 days before they expired. In experiment 1 in Table A, the example relied upon by the Examiner as evidencing a synergistic effect, the mice survived about 5 days longer for a total of 17 days.

In comparison, in the examples provided in the present specification in Table IV, the mice treated with CPT-11 alone survived for at least 26 days. (The data in Table IV is not directed to days of survival as in Furuta, but is instead directed to the time in days for the tumors to reach 1000 mg. Therefore, presumably, the mice lived longer than is reported.) The mice treated with doxorubicin alone survived for at least 24 days. The mice that were treated with a synergistic combination of CPT-11 and doxorubicin survived for at least 52 days. The rate of survival for mice treated with the synergistic combination is almost double the rate of survival for the mice treated with the individual constituents alone.

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As explained above, Furuta fails to determine the HNTD for CPT-11 and adriamycin, and therefore one of ordinary skill in the art cannot conclude that the results reported by Furuta demonstrate a synergistic effect as defined by the presently claimed invention. Moreover, Furuta conducts all of his experiments on leukemia cells in mice. Furuta does not teach a composition that provides a synergistic effect in the treatment of solid tumors, as presently claimed. For at least these reasons, Furuta does not anticipate the claimed invention.

REJECTION UNDER 35 U.S.C. § 103(a)

The Examiner also maintains the rejection of claims 5, 8, and 13-20 under 35 U.S.C. § 103(a) over Furuta.³

With regard to claims 5 and 7, the Examiner argues that Furuta teaches adriamycin and etoposide, which are both well known anthracycline antibiotics or antitumor agents of very similar structure. Final Office Action at 3. With regard to claim 13, the Examiner argues that the “difference between applicant’s claimed method and the method taught by Furuta et al. is that the applicant’s type of tumor that is treated.” *Id.* at 4. Because Furuta teaches a method for treating a leukemia tumor, the Examiner argues that it would have been obvious to treat other tumors, such as solid tumors, using the antitumor agents taught in Furuta “based on need, like the type and/or degree of severity of the tumor.” *Id.* at 5.

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3 Applicant notes that in the discussion of this particular rejection, the Examiner refers to claim 7 when discussing epipodophyllotoxin teniposide. Final Office Action at 3. In order to clarify the record, epipodophyllotoxin etoposide is recited in claim 7 and epipodophyllotoxin teniposide is recited in claim 8, which is listed in the formal rejection.

To establish a *prima facie* case of obviousness, the reference must teach or suggest all the claim elements or must provide some suggestion or motivation to one of ordinary skill in the art to modify the reference. Additionally, there must be a reasonable expectation of success. M.P.E.P. § 2143 (8th ed. 2001). Applicant respectfully traverses the rejection and submits that Furuta would not have rendered obvious the claimed invention.

Claims 5 and 7 (and 8) indirectly depend from independent claim 1 and are therefore patentable for the same reasons as claim 1. Because, as discussed above, Furuta does not teach determining the HNTD of either CPT-11 or adriamycin alone, or finding a combination that provides a therapeutic effect that is superior to one of these doses, Furuta does not suggest a synergistic composition according to the present claims. For at least this reason, Furuta fails to render the presently claimed invention obvious.

Furthermore, in rejecting the claims under 35 U.S.C. § 103(a), the Examiner fails to indicate where or how Furuta provides a reasonable expectation of success in achieving a synergistic composition that is useful in treating solid tumors. Furuta discloses treatment of leukemias. Furuta does not disclose or suggest treating solid tumors with CPT-11 and adriamycin. The Examiner minimizes this omission, asserting that one would apply the teachings of Furuta to any type of tumor. Applicant respectfully disagrees.

It is widely recognized in the art of tumor therapy that a treatment regimen that is successful against one type of tumor (*e.g.*, leukemias) will not necessarily be successful against other types of tumors (*e.g.*, solid tumors). Thus, even assuming for the sake of argument that one were to be motivated by Furuta to apply the teachings of Furuta to

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other cancers, such as solid tumors, that person would have no reasonable expectation of success in treating the solid tumors. This is especially so because Furuta does not teach or suggest how to determine the HNTD nor how to use that information to arrive at the most efficacious combination dose.

Rather, at most, one of skill in the art would see Furuta as a mere invitation to attempt to treat solid tumors, not a guarantee of success. In other words, any motivation that Furuta might provide would be a motivation to try, not a motivation to succeed. M.P.E.P. § 2145 X.B. prohibits rejections under this theory. Indeed, it is only through the teachings of the present specification that one of ordinary skill in the art would gain a reasonable expectation of success in treating solid tumors with a synergistic combination of camptothecin, or a camptothecin derivative, and a topoisomerase II inhibitor. However, as mentioned above, Applicant's own disclosure cannot provide the motivation or expectation of success necessary to render a claim obvious.

Therefore, because Furuta does not provide an adequate motivation or reasonable expectation of achieving the presently claimed invention, Applicant respectfully submits that the presently claimed invention would not be obvious over Furuta.

CONCLUSION

In view of the foregoing remarks, Applicant respectfully requests reconsideration of the application, and the timely allowance of the pending claims.

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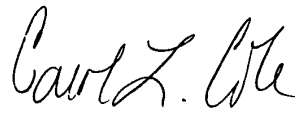
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Respectfully submitted,

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Attachments

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DOXORUBICIN et IRINOTECAN: MTD (iv - ip) chez la SOURIS

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Databases: GPLD, Cancerlit, Embase, Biosis

DOXORUBICIN

Differential uptake of 1-(2-chloroethyl)-3-(trans-4-methylcyclohexyl)-1-nitrosourea and doxorubicin by Lewis lung carcinoma and Ridgway osteogenic sarcoma

- ✓ Schmid, Otter, Perri, Hutchison, and Philips.
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Cancer-Res 1983.VOL: 43 (3).P: 976-979.

The compound 1-(2-chloroethyl)-3-(trans-4-methylcyclohexyl)-1-nitrosourea (MeCCNU), a lipophilic substance, is therapeutically effective against many murine tumors, especially Lewis lung carcinoma (LL), but is surprisingly ineffective against Ridgway osteogenic sarcoma (ROS). Most alkylating agents and doxorubicin (DX) are active against ROS but have relatively little therapeutic activity against LL; most are water soluble. We have analyzed these differences further by measuring blood and tumor concentrations of MeCCNU and DX in LL- and ROS-bearing mice (C57BL/6J x DBA/2 F1 and AKR/J x DBA/2J F1, respectively) after **ip injection of the maximum tolerated doses** (MeCCNU, 40, and DX, 15 mg/kg). MeCCNU blood levels were similar in the two tumor-bearing strains, falling rapidly from 12- to 1.8-ug equivalents/ml between 1 and 6 hr and to zero by 24 hr. DX plasma levels were also similar in the two mouse strains. Presumably, differences in drug concentrations and half-life in the circulation are not the cause of the differential sensitivity. Tumor levels were more illuminating. MeCCNU concentrations were three-fold higher in LL than in ROS. At 1, 3, 6, and 24 hr, the levels in ug equivalents/g were, respectively, 20, 13, 5, and 1.5 in LL and 5, 3, 2, and 1.7 in ROS. Conversely, ROS had approx 50% higher concentrations of DX than did LL at each time interval. It was noted in MeCCNU assays that LL contained significantly more ether-extractable lipids than did ROS (3.1 \pm 0.4 versus 0.67 \pm 0.2 mg/g). The above results suggest that LL and ROS differ in sensitivity to the two drugs because of differences in uptake that may be related to differences in lipophilicity of the drugs and lipid content of the tumors.

Development of a panel of 15 human ovarian cancer xenografts for drug screening and determination of the role of the glutathione detoxification system

- ✓ Kolfsochten, G. M., Pinedo, H. M., Scheffer, P. G., Schlueper, H. M., Erkelens, C., and Boven, E.
Department of Medical Oncology, University Hospital Vrije Universiteit, Amsterdam, 1081 HV, The Netherlands
Gynecologic oncology 2000 Mar.VOL: 76 (3).P: 362-8.

OBJECTIVES: We have established a panel of 15 human ovarian cancer xenografts grown subcutaneously in the flank of the nude mouse. Similar to the clinic, the xenografts show differences in histological subtype and volume doubling time. We determined whether the panel is useful for drug screening by testing the sensitivity to six conventional anticancer agents. In addition, we investigated whether the glutathione detoxification system affects sensitivity to cisplatin and cyclophosphamide, major drugs in the treatment of ovarian cancer. **METHODS:** Mice bearing well-established tumors were treated at **maximum tolerated doses** as defined by a reversible weight loss up to 15% of their initial weight: cisplatin 5 mg/kg iv weekly x2, cyclophosphamide 150 mg/kg ip 2-weekly x2, **doxorubicin 8 mg/kg iv weekly x2**, hexamethylmelamine ip 150 mg/kg every other day x4, methotrexate ip 150 mg/kg weekly x2, and 5-fluorouracil 60 mg/kg ip weekly x4. Glutathione levels and the activities of three different glutathione-dependent enzymes were measured in untreated xenograft tissues. **RESULTS:** Growth inhibition >75% was reached for cisplatin in 40%, for cyclophosphamide in 27%, and for doxorubicin in 20% of the xenografts. Methotrexate and 5-fluorouracil did not induce growth inhibition of importance. Hexamethylmelamine showed >75% growth inhibition in 53%

of the xenografts, which may have been caused by the favorable metabolism of the drug in mice when compared with that in patients. Glutathione levels varied 3.6-fold in the xenografts and did not show a relation with sensitivity to cisplatin, cyclophosphamide, or doxorubicin. No relation was found between the activities of glutathione S-transferase and glutathione peroxidase and the sensitivities to the three anticancer agents. Glutathione reductase activity, however, showed a weak, inverse relation with the efficacy of cisplatin and cyclophosphamide (r values of -0.55 and -0.58, respectively). **CONCLUSIONS:** The sensitivity to the six anticancer agents of our panel of 15 human ovarian cancer xenografts reflects the response rates known for similar drugs in ovarian cancer patients. In that respect, the panel may be useful for drug screening as well as studies on the relevance of drug resistance features in vivo. The various components of the glutathione detoxification system did not predict for primary drug resistance which confirms clinical data in ovarian cancer

IRINOTECAN

Comparison of intraperitoneal and intravenous administration of irinotecan (CPT-11) in a murine peritoneal colon 26 model

✓ Guichard, S., Chatelut, E., Bugat, R., Mahjoubi, M., and Canal, P.

Centre Claudius-Regaud, Toulouse, France

Proc Am Assoc Cancer Res 1997; 38(3): 305.88th Annu Meet Am Assoc Cancer Res (AACR). San Diego (Apr 1997) .Abs: 2047.

In order to assess the potential benefits of ip administration in tumor located in peritoneal cavity, the efficacy of CPT-11 was evaluated in a murine tumor model obtained after ip injection of 10sup6 (day 0) colon 26 cells. CPT-11 was injected **ip** or **iv** (days 2, 6 and 10) to balb/c mice bearing tumor at total doses ranging from 50 to 800 mg/kg. After **ip** administration, the increase in Life Survival (ILS%) was 177% at the **maximum tolerated dose (MTD)** of **600 mg/kg**, whereas after **iv** administration, ILS was only 77% at the **MTD** of **300 mg/kg**. The pharmacokinetics of both CPT-11 and its active metabolite SN-38 were compared after single iv or ip injection of 66 mg/kg of CPT-11. Peritoneal AUC of CPT-11 was about 15 fold greater after ip than after iv administration. Peritoneal and plasma AUC of SN-38 after ip administration did not differ significantly to those after iv administration. Plasma CPT-11 maximal concentrations were significantly higher after iv than after ip administration but plasma CPT-11 AUCs were identical. Then, the high level of toxicity after iv administration might be due to the high plasma maximum concentrations of CPT-11. The better efficacy after ip administration seemed to be due to both better tolerance and larger peritoneal concentrations for CPT-11